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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,592	02/02/2006	Venkata Satya Nirogi Ramakrishna	SUB 0005 US	9209

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EXAMINER	
YOUNG, SHAWQUIA	
ART UNIT	PAPER NUMBER
1626	
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02/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,592	RAMAKRISHNA ET AL.	
	Examiner	Art Unit	
	SHAWQUIA YOUNG	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *5-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are currently pending in the instant application.

I. *Priority*

The instant application is a 371 of PCT/IN03/00370, filed on November 25, 2003 and claims benefit of Foreign Application INDIA 883/MAS/2002, filed on November 28, 2002.

II. *Restriction/Election*

A. Election: Applicant's Response

Applicants' election without traverse of Group I in the reply filed on January 2, 2008 is acknowledged.

Subject matter not encompassed by elected Group I are withdrawn from further consideration pursuant to 37 CFR 1.142 (b), as being drawn to nonelected inventions.

III. *Rejections*

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula (I) or stereoisomers, geometric forms, radioisotopes, N-oxide or prodrugs does not reasonably provide enablement for solvates, polymorphs or metabolites of a compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case

The nature of the invention

The nature of the invention is a compound of formula (I), its stereoisomers, its radioisotopes, its geometric forms, its N-oxide, its polymorphs,

its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, its useful bioactive metabolites, any suitable combination of the above.

The state of the prior art

It is the state of the prior art that the term "solvate" found in the claims is defined as a compound formed by solvation (the combination of solvent molecules with molecules or ions of the solute. It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compound (See *Vippagunta, et al.*)

The scope of "solvate" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Solvates and hydrates cannot always be predicted and therefore are not capable of being claimed if the applicant cannot properly enable a particular hydrate or solvate.

The term "metabolite" is defined as any substance produced or used during metabolism (digestion). In drug use, the term usually refers to the end product that remains after metabolism and one does not really know what happens to the metabolite after it is in our body and thus renders unpredictability in the art. According to Prueksaritanont, *et al.*, if a metabolite is less stable

chemically than its parent, administration of the metabolite may lead to more limited distribution of the metabolites than is the case when the parent is dosed. The distribution of a metabolite formed *in vivo* is expected to be dependent on the tissue distribution of both the parent drug and the metabolizing enzymes responsible for the parent-to-drug conversion. Furthermore, there are cases when the generated metabolite, because of its instability, leads to regeneration of the precursor within the body. Also, the distribution of an administered metabolite to organs and tissues may be more limited than when the metabolite is formed *in vivo* and thus may restrict potential toxicities to limited tissues as compared to that generated from the parent compound. Additionally, metabolites are generally more polar than their parent compounds and once formed *in vivo*, have a greater potential to accumulate inside the cells due to the larger permeability barrier to transverse out of cells. This factor causes an increase in chances for toxicity produced by the metabolite.

It is the state of the prior art that the term "polymorphism" is defined as the existence of different solid forms (modifications) of a compound which have the same chemical composition but different structures and thus different physical and sometimes also chemical properties (Concise Encyclopedia Chemistry 1993). It is the state of the prior art that under any given pressure and temperature, other than the conversion points, only one modification is stable, the one with the lowest vapor pressure. Often the conversion rate in the solid phases is so slow that even modifications which are unstable under the conditions can be kept for a long time in their metastable state. This conversion

rate can depend on the rate of temperature change or pressure change (Concise Encyclopedia Chemistry 1993). As defined, the instant claims read on any polymorph of the claimed compound which is broader than the enabling disclosure. There is no support or guidance to show that one can even make a polymorph of the instant compounds and would therefore require undue experimentation.

The amount of direction or guidance present and the presence or absence of working examples

There is little direction or guidance present in the specification or working examples present in the specification are that defines or relates to what polymorphs, solvates and metabolites, or any suitable combination of the above are being included in the elected invention. The term "solvates" is discussed on page 20 of the specification and reads on the following:

> The pharmaceutically acceptable salts of compounds of formula (I) may exist as solvates, such as water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent preparation or crystallization, or adventitious to such solvent.

The breadth of the claims

The breadth of the claims is a compound of formula (I), its stereoisomers, its radioisotopes, its geometric forms, its N-oxide, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, its useful bioactive metabolites, any suitable combination of the above.

The quantity of experimentation needed and the level of the skill in the art

While the level of the skill in the pharmaceutical art is high, the quantity of experimentation needed is undue experimentation. One of skill in the art would need to prepare compounds with both similar and different structural radicals without any direction as to what structural radical is needed and how different the metabolites, for example, can be from a compound of formula (I).

The level of skill in the art is high without showing or guidance as to how to make metabolites, solvates or polymorphs or any suitable combination of the above of a compound of formula (I) it would require undue experimentation to figure out the starting materials, solvents, temperatures and reaction times that would provide metabolites, solvates or polymorphs of the above compounds.

To overcome this objection, Applicant should submit an amendment deleting the terms "metabolites, solvates and polymorphs".

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula (I) or stereoisomers, nitrogen oxides or a pharmaceutically acceptable salt does not reasonably provide enablement for a hydrate of a compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in

scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case

The nature of the invention

The nature of the invention is a compound according to claim 1,which is selected from the list as shown in claim 2, a stereoisomer, or a polymorph, or any suitable combination of above such as a nitrogen oxide thereof, a prodrug of the compound or the nitrogen oxide, a pharmaceutically acceptable salt of the compound, the nitrogen oxide, or the prodrug, or a solvate or hydrate of the compound, the nitrogen oxide, the prodrug or the pharmaceutically acceptable salt.

The state of the prior art

It is the state of the prior art that the term "hydrate" found in the claims is defined as a compound formed by solvation (the combination of water molecules with molecules or ions of the solute. It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. Predicting the formation of hydrates of a compound and the number of molecules of water incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of hydrates and hence generalizations cannot be made for a series of related compound (See *Vippagunta, et al.*)

The scope of "hydrate" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Hydrates cannot be predicted and therefore are not capable of being claimed if the applicant cannot properly enable a particular hydrate.

The amount of direction or guidance present and the presence or absence of working examples

There is little direction or guidance present in the specification or working examples present in the specification are that defines or relates to what hydrates are being included in the elected invention. The term "hydrates" are discussed in relation to "solvate" on page 20 and reads on the following:

> The pharmaceutically acceptable salts of compounds of formula (I) may exist as solvates, such as water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent preparation or crystallization, or adventitious to such solvent.

The breadth of the claims

The breadth of the claims is a compound according to claim 1,which is selected from the list as shown in claim 2, a stereoisomer, or a polymorph, or any suitable combination of above such as a nitrogen oxide thereof, a prodrug of the compound or the nitrogen oxide, a pharmaceutically acceptable salt of the compound, the nitrogen oxide, or the prodrug, or a solvate or hydrate of the compound, the nitrogen oxide, the prodrug or the pharmaceutically acceptable salt.

The quantity of experimentation needed and the level of the skill in the art

The level of skill in the art is high without showing or guidance as to how to make hydrates of a compound of formula (I) it would require undue experimentation to figure out the starting materials, solvents, temperatures and reaction times that would provide hydrates of the above compounds.

To overcome this objection, Applicant should submit an amendment deleting the term "hydrate".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as

being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically for the following limitation in claims 1 and 2: "any suitable combination of above such as a nitrogen oxide thereof". It is unclear what subject matter is embraced by the above limitation and the claims or disclosure do not clearly define the limitation to know the metes and bounds of "any suitable combination of above such as a nitrogen oxide thereof". Applicants are suggested to delete the phrase "any suitable combination of above such as a nitrogen oxide".

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants are claiming a "prodrug of the compound or the nitrogen oxide" (page 15, line 8). Then line 9 contains the limitation "or the prodrug" and line 10 contains the limitation "the prodrug or the pharmaceutically acceptable salt". It is unclear what Applicants are trying to claim with the various references to "prodrug". Are Applicants claiming "a prodrug" of the compounds listed when stating prodrug three different times in the claim. Or are Applicants referring to the prodrug of a pharmaceutically acceptable salt of the compound (line 9) and the prodrug of a solvate or hydrate of the compound (line 10)? It is confusing because the first reference is to "a prodrug" whereas the other two references are to "the prodrug". The term "the prodrug" usually means that a reference is being made to the term "a prodrug" and is claiming the same subject matter as the term "a prodrug". Since there is only support for stereoisomers and pharmaceutically acceptable salts, the other phrases and

terms at the end of the claim should be deleted. The claim should read ... --or a stereoisomer or pharmaceutically acceptable salt thereof—.

Claim 2 states it could have a hydrate of the instant compounds, however, claim 2 depends on clam 1 and there is no antecedent basis for hydrate in claim 1.

IV. *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 6:30 AM-3:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph M^{c}Kane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shawquia Young/
Examiner, Art Unit 1626

/Joseph K McKane/

Supervisory Patent Examiner, Art Unit 1626